

## COMMENTARY

# Vigilance is not enough

Global surveillance is key to tracking potential pandemic viruses such as H5N1. But we need to share samples more rapidly, increase testing in endemic areas and track more than one virus, argues **Walter Boyce**.

**A**nother influenza pandemic seems inevitable, and without a generic vaccine, our best chance of being prepared is to identify, track and stop the spread of viruses such as highly pathogenic H5N1. Two years ago, some believed that H5N1 viruses were poised to spread around the globe on the wings of migrating wild birds. A massive effort was mounted to track their movement but, as of September 2007, very few positive birds have been found in tests of over 300,000 healthy wild birds from more than 40 countries<sup>1</sup>. Several hundred infected birds (almost all of them dead) were found in endemic and outlying areas, but dead birds do not tell us about the birds that don't get sick when infected — those that could spread H5N1 over longer distances.

We shouldn't be surprised that random sampling failed to detect what is apparently a rare event: active H5N1 infection in migrating, healthy wild birds. And failing to find H5N1 can be good news if the goal is early detection in non-endemic areas, as it was for many of the wild birds sampled in Europe and the United States.

But it is troubling that we still don't understand the importance of wild birds in the replication and spread of H5N1 within and between countries and continents. Each new virus outbreak, such as that in free-range poultry in the United Kingdom last month, is followed by uncertainty and speculation about the source and transmission route: is it wild birds or poultry? Knowing the source won't change the immediate response — new outbreaks, like fires, must be stamped out — but it will guide efforts aimed at preventing further outbreaks. For example, moving free-range poultry indoors to separate them from wild birds makes sense if wild birds are a risk. But keeping poultry indoors won't prevent an outbreak if the transfer of infected poultry is responsible.

There is growing recognition that it is time to change our surveillance approach to H5N1 and the other influenza subtypes that could cause the next pandemic. Here are three steps that can move us forward.

First, we must improve our ability and willingness to rapidly share data and samples. Despite calls for a more open approach by researchers such as Ilaria Capua at the National



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**No access: only by sharing data from local bird-flu outbreaks can global agencies prepare for a pandemic.**

Reference Laboratory for Avian Influenza and Newcastle Disease in Padova, Italy, there are still substantial obstacles to the rapid sharing of data and samples, whether they are from wild birds or poultry. Regulatory problems hinder shipping of these samples between countries — it can take weeks to months to arrange for the proper import/export permits, and some countries do not allow any samples to be analysed outside their borders. It is also difficult to balance rapid public release of data with appropriate protection of intellectual-property rights.

But attitudes are changing, as shown by the creation of the Global Initiative on Sharing Avian Influenza Data (GISAID), an organization designed to unite researchers and promote data sharing. In 2005, the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization (FAO) created the OFFLU avian influenza network to facilitate the collection and exchange of viruses and the deposition of sequences in genome banks. And in the United States, the National Institute of Allergy and Infectious Diseases (NIAID) has an established policy of releasing influenza genome data to GenBank and other public sites within 45 days of being generated.

On the wild-bird front, the US Agency for

International Development and the Centers for Disease Control and Prevention have entered into a unique public-private partnership with the Wildlife Conservation Society, a non-governmental organization now charged with managing the Global Avian Influenza Network for Surveillance (GAINS). This initiative aims to establish a global collaborative network for sharing data, including all influenza subtype samples, through an open-access database available to anyone<sup>2</sup>.

## Swapping data

Although these and other approaches and policies are important, it is ultimately up to the researchers on the front lines to ensure that data and samples make it into the pipeline as quickly as possible. Because isolating viruses is such hard work and because the resulting samples can yield a wealth of information and publications over time, there may be a tendency to view viruses in the freezer as money in the bank — a rich resource to be guarded and tapped later. This approach does not enhance pandemic preparedness, and future publications won't seem so important in the middle of a roaring pandemic. We simply must do a better job, and making data release within 45 days a community standard would be a step in the right direction.

Second, we must unravel the role of wild-bird

**"Future publications won't seem so important in the middle of a roaring pandemic."**





Live birds pose a greater threat of transmitting the flu virus than dead birds (inset).

species in spreading H5N1 by improving our wild-bird surveillance and research efforts. It is clear that wild aquatic birds are a natural reservoir of influenza viruses, although it is possible that H5N1 persists in a wild-bird species we wouldn't normally suspect. But we don't know whether H5N1 viruses are endemic in wild-bird populations or if infections in wild birds represent spillover from poultry. And although movement of infected poultry plays a pivotal part in spreading H5N1 to new areas, we continue to debate, year after year, the risk to poultry posed by migrating wild birds.

To move beyond debate and come up with definitive answers, we must investigate H5N1 in the areas where virus transmission actually takes place. Until recently, most wild birds tested for H5N1 had been sampled in regions of Europe and North America where infections are rare or absent. Dead birds, such as swans, have been conspicuous sentinels of H5N1 infection in Europe, triggering rapid responses to prevent the spread to poultry. But we don't know how these birds acquired their infections, and the presence of infected dead birds doesn't necessarily mean that virus transmission is occurring, or will occur, in the area where they are found.

### A live problem

It is live birds, not dead birds, that shed the virus and pose a threat. Because our surveillance efforts have struggled to find infected live birds in non-endemic regions, it is essential that we shift sufficient resources and efforts to evaluate H5N1 transmission in wild birds in known endemic areas such as southeastern Asia, China, Indonesia and Africa.

This is not a trivial task, but encouraging signs are emerging. For example, the FAO in collaboration with national veterinary serv-

ices and wildlife institutions launched a wild-bird surveillance programme in 2006 in Eastern Europe, the Middle East and Africa<sup>3</sup>. And the GAINS programme, involving dozens of governmental, non-governmental, as well as academic partners, is now working in almost 30 countries, including Cambodia, Mongolia, Vietnam and Indonesia.

Early detection programmes in non-endemic regions are valuable and must continue alongside efforts in endemic areas. But when the data are mostly negative, it is no simple matter to develop a systematic, science-based programme. Risk assessments, such as those performed in the United Kingdom by the Department for Environment, Food and Rural Affairs<sup>4</sup>, help improve surveillance efforts because they specifically consider the ecology and movements of high-risk bird species relative to known outbreaks of H5N1. These assessments, and the value of wild-bird surveillance in general, could be markedly improved by sampling birds at the beginning and end of their migratory journeys from endemic areas.

Third, we need to improve our ability to diagnose and characterize all virus subtypes from wild birds. H5N1 viruses are not the only pandemic threat, and this provides a compelling reason to identify and track the movement of other influenza viruses as well. We need vaccines that protect us against all of the influenza subtypes that nature might throw in our direction. The global human population is immunologically naive to at least 12 viral subtypes in addition to H5, and we don't know which virus will cause the next pandemic, or the one after that. Besides H5, today's 'short list' should include H2, H6, H7 and H9. We must look beyond H5N1 and conduct surveillance that

captures the full list of viral genetic diversity — and feed those data into the development of effective pandemic vaccines.

We don't have to look far. Depending on species, location and season, up to 25% of the wild birds sampled in the past two years were infected with non-H5N1 influenza viruses. The early detection efforts in North America and Europe may have failed to find H5N1, but they did an excellent job of sampling other influenza viruses. Unfortunately, too many of these viruses were discarded and their information lost forever once samples were classified as non-H5N1. This is

not good enough. We must evaluate the pandemic potential of all the influenza subtypes detected during surveillance.

It won't be easy or inexpensive. The OIE has only seven dedicated laboratories worldwide that diagnose H5N1 and other avian influenza viruses, with additional testing done in some national and private laboratories. Unfortunately,

our ability to detect and identify the full range of viruses is limited because the diagnostic reagents and procedures used today were primarily optimized for identifying influenza viruses in poultry, not wild birds.

For example, virus isolation is the only available method that allows complete characterization and genetic sequencing. This procedure, typically done by inoculating wild-bird virus samples into chicken eggs, is time-consuming, expensive, requires special biosafety considerations and, importantly, might not work at all with some wild-bird viruses. Several laboratories are working on this problem, but resources are limited, and there is still an urgent need to develop and validate diagnostic tests specifically for wild birds.

The inconvenient truth is that our close relationship with domestic animals and wildlife puts us at increasing risk of an influenza pandemic, and, short of developing a vaccine, our best option is surveillance. The immediate pandemic threat being tossed our way is H5N1, but other viruses are lurking, and we had simply better be looking in the right direction, and working together, if we hope to catch the flu before it catches us. ■

Walter Boyce is director of the Wildlife Health Center, and co-director of the NIH Center for Rapid Influenza Surveillance and Research, at the School of Veterinary Medicine, University of California, Davis, California, USA.

1. [http://www.fao.org/docs/eims/upload/231765/EW\\_Europe\\_aug07\\_ai.pdf](http://www.fao.org/docs/eims/upload/231765/EW_Europe_aug07_ai.pdf)
2. <http://www.gains.org/>
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4. <http://www.defra.gov.uk/animalh/diseases/monitoring/pdf/qra-recentdevelopments120707.pdf>